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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MERTZ, PREMA MARIA	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 12/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/727,514	THEZE ET AL.	
	Examiner	Art Unit	
	Prema M. Mertz	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 26-49 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 26-49 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 3/5/04, 12/5/03.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-25 have been canceled and new claims 26-49 (3/5/2004) have been added. Claims 26-49 are pending and under consideration by the Examiner.

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. It is suggested that the title be amended to only recite "peptides of IL-2".

Claim Rejections - 35 USC § 112, first paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3a. Claims 26, 28-36, 37, 39-49, are rejected under 35 U.S.C. 1 12, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a peptide which is a derivative of a particular disclosed sequence (SEQ ID NO:2 or 4). The claims do not require that the peptide possess any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of peptides that are defined only by sequence identity. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics

of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a partial function. There is not even identification of any particular portion of the structure that must be conserved for the biological activity of binding to the IL-2β chain or the monoclonal antibodies produced by H2-8 hybridoma. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics and structure/function relationship, the specification does not provide adequate written description of the claimed genus.

Vas-cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the ad that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the written description' inquiry, whatever is *now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Therefore, only a peptide of amino acid sequence set forth in SEQ ID NO:2 or 4 as recited in the claims, but not the full breadth of the claims meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

3b. Claim 26 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The hybridoma cell line recited in claim 26 is essential to the claimed invention. The reproduction of antibodies from the disclosed hybridoma is an extremely unpredictable event. The hybridoma H2-8 must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The instant specification does not disclose a repeatable process to obtain the hybridoma, and it is not apparent if the hybridoma is readily available to the public. If the deposits have been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridoma has been deposited under the Budapest Treaty and that the hybridoma will be irrevocably and without restriction or condition be released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808.

Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or for the enforceable life of the patent whichever is longer. See 37 CFR 1.806. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

Amendment of the specification to disclose the date of deposit and the complete name and address of the depository is required.

If the deposit was made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the hybridomas described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to *In re Lundak*, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985), and 37 CFR 1.801-1.809 for further information concerning deposit practice.

3c. Claims 26-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a purified peptide consisting of the amino acid sequence set forth in SEQ ID NO:2 or 4 does not reasonably provide enablement for a purified peptide having SEQ ID

NO:2 or a derivative thereof or a homologous peptide thereof or a peptide that has a sequence of SEQ ID NO:4 or a derivative thereof or a homologous peptide thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 26, for example, is overly broad in its limitation of "derivative thereof" because no guidance is provided as to which of the myriad of peptide molecules encompassed by the claims will retain the characteristics of the desired peptide which binds to the IL-2β chain or the monoclonal antibodies produced by H2-8 hybridoma. Variants of a peptide can be generated by deletions, insertions, and substitutions of amino acids, but no actual or prophetic examples on expected performance parameters of any of the possible variants of the claimed peptide molecule or muteins of the peptide molecule have been disclosed. Furthermore, it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Mikayama et al. (1993) teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page 10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape

characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

There is no guidance provided in the instant specification as to how one of skill in the art would generate and use a derivative peptide of SEQ ID NO:2 or SEQ ID NO:4 exemplified in the specification. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Given the breadth of the claims, in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claims 26-49 are drawn to a peptide which is a species homologue of the peptide of SEQ ID NO:2 or SEQ ID NO:4. The specification provides only sequence data to allow one to characterize these peptides (see pages 31-32, Example 8). Many distinct peptides may share the same activity, so that even if one were to determine a biological activity of the peptide, say binding to IL-2β, many distinct peptides could have this activity. As a result, if one were to

isolate a peptide from a different species that had the same activity, one could not reasonably predict if the isolated peptide was a species homologue of the original peptide because one could not determine if the sequence difference between the original and isolate were due to species differences or to the peptides being non-homologous but sharing the same activity. Even though assays are provided to test for the desired activities (Example 8, pages 31-32), it would be undue experimentation to conduct every assay for every peptide in the hopes of identifying a specific activity, and no guidance is provided to enable a skilled artisan to predict which activity the peptide is likely to have. Further, the specification provides insufficient guidance to allow one to obtain species homologues. Additionally species homologues often display low sequence identity so that identification based solely on sequence similarity is impossible. Under such common circumstances, if one cannot test for the expected activity of the encoded putative species homologue, then it is impossible to identify species homologues. For example in The Cytokine Facts Book (1994), Robin Callard and Andy Gearing. Academic Press Inc. San Diego, CA, the amino acid sequence of IL-2 (interleukin-2) from human compared to mouse differs by 16 amino acids in length (page 39, table) and share only about 60% identity (page 39, "Crossreactivity" section). Based solely on sequence, it would be clearly impossible for one skilled in the art to identify the mouse and human proteins as species homologues; however, when one is able to compare a known or putative activity (page 39, "Bioassays" section"), identity can be confirmed.

Furthermore, Reeck et al. (line 1-2) point out, ""Homology" has the precise meaning in biology of "having a common evolutionary origin,"...".

It is stated at the top of column 2 that:

A similarity, then, can become a fully documented, simple fact. On the other hand, a common evolutionary origin must usually remain a hypothesis, supported by a set of arguments that might include sequence or three-dimensional similarity. Not all similarity connotes homology but that can be easily overlooked if similarities are called homologies. Thus, in this third case, we can deceive ourselves into thinking we have proved something substantial (evolutionary homology) when, in actuality, we have merely established a simple fact (a similarity, mislabeled as homology). Homology among similar structures is a hypothesis that may be correct or mistaken, but a similarity itself is a fact, however, it is interpreted.

Reeck et al. provided emphasis to the above reasons for not being able to identify, if one is able to isolate candidates, species homologues as claimed because of the lack of guidance and information in the current specification.

With respect to the term "conservative substitutions" recited in claims 28 and 39, the claims are overly broad since no guidance is provided as to which of the myriad of peptide species encompassed by the claims will retain the desired biological properties and the claims broadly encompass a significant number of inoperative species. The specification (pages 8-9; pages 11-14) merely outlines residues which are considered conservative. This is not adequate guidance as to the nature of the peptide analogues or variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Therefore Applicants have not presented enablement commensurate in scope with the claims.

3d. Claims 26-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a purified peptide consisting of the amino acid sequence set forth in SEQ ID NO:2 or 4 which binds to the IL-2β chain, does not reasonably provide enablement for a peptide "capable of" binding to the IL-2β chain, as recited in claim 26. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification is non-enabling for peptides that do not bind and are only capable of binding if further modified such that they can then bind, because applicants have not taught how to further modify the peptide molecules such that they can bind to its target. It has been held that an element is "capable of" performing a function is not a positive limitation but only requires the ability to perform. It does not constitute a limitation in any patentable sense. *In re Hutchison*, 69 USPQ 138.

Claim rejections-35 USC § 112, second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-49 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 26, 27, 37, and 38 recite the limitations "has" or "having". It is unclear whether this language is open or closed language. It is suggested that the claims be amended to recite the conventional "consisting of" language.

Claims 28 and 39 recite the limitation "said homologous peptide" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 48-49 are vague and indefinite because the term "homologous" has been mis-spelled.

Claims 29-36, 40-47, are rejected under 35 U.S.C. § 112, second paragraph, insofar as they depend on the above rejected claims for their limitations.

Claim rejections-obviousness type double patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 26-49 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-10 of U.S. Patent No. 6,825,334 ('334). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 3-10 of U.S. Patent No. '334 (having all common inventors with the instant application), claim a peptide encoded by a polynucleotide having at least 75%, 80%, 90% or

95% identity to SEQ ID NO:1 or SEQ ID O:3. In the instant claims, a peptide of SEQ ID NO:2 or 4, or a derivative of these peptides is claimed. The instant claims are species claims of the patent claims and encompass subject matter to which the allowed claims are generic because the peptides in the patent are being claimed based on the polynucleotide encoding the peptides. However, the instant claims are obvious from the patented claims because the instant claims are directed to specific embodiments encompassed by the patented claims. The instantly claimed products are included in the patented claims. It would have been obvious to one of ordinary skill in the art at the time the present invention was made, that the patented claims are included in the instant claims because a polynucleotide can be translated in three reading frames. The patented claims if infringed upon would also result in infringement of the broad claims of the instant application. Allowance of the pending claim, therefore, would have the effect of extending the enforceable life of the allowed claims beyond the statutory limit.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 26-28, 37-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Taniguchi et al (U.S. Patent No. 4, 738, 927).

The reference discloses a cDNA encoding human IL-2 and the protein encoded thereby which was isolated (see abstract; columns 5-6). Amino acid Sequence I (Figure 2B) of the reference discloses a purified peptide having the amino acid sequence of SEQ ID NO:2 or SEQ

ID NO:4 or derivatives thereof. Furthermore, the reference discloses that muteins of the IL-2 protein are encompassed by the scope of the invention (see column 10, lines 17-66; column 11, lines 1-6) such that IL-2 muteins with IL-2 activity of binding to the IL-2β chain are maintained. Since the term "having" has been interpreted by the Examiner as being open language, the peptide disclosed in the reference meets the limitations of a purified peptide "having" SEQ ID No:2 or SEQ ID NO:4 or derivatives thereof. Therefore, the polypeptide disclosed in the reference meets the limitations of claims 26-28, 37-39.

Claim rejections-35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 29-36, 40-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taniguchi et al (U.S. Patent No. 4, 738, 927).

The teachings of Taniguchi et al. have been set forth above in paragraph 6 above. However, Taniguchi does not teach the specific mutations in IL-2 protein as recited in claims 29-36, 40-49. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant invention was made to create mutations in the IL-2 protein, to determine the steric effects of these amino acids substitutions on the activity of the IL-2 protein. Creating mutations in the IL-2 protein by employing those methods that were old and well known in the art of

molecular biology at the time that the instant invention was made would have been *prima facie* obvious to an artisan in light of the Taniguchi reference because Taniguchi teaches that some substitutions cause the structure of the IL-2 protein to remain unchanged (see column 10, lines 21-26) while other substitutions in the IL-2 protein may be important in enhancing the function of the IL-2 protein (improved muteins) or in obtaining muteins with additional desired functions as set forth in claims 48-49.

Conclusion

Claims 26-49 are rejected.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (571) 272-0829.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Prema Mertz

Prema Mertz Ph.D.
Primary Examiner
Art Unit 1646
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